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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/664,801	09/17/2003	Torben Halkier	4614-0120P	3913

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 12/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/664,801	HALKIER ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58,59,61,62 and 65-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58,59,61,62 and 65-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendment filed 21 September 2006 has been entered in full. Claims were 57, 60, 63 and 64 are canceled. New claims 67-70 are added. Claims 58, 59, 61, 62, 65-70 are pending and under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The specification is in compliance with 37 CFR 1.821-1.825 of the Sequence Rules and Regulations.

The rejection to claims 57, 60, 65 and 66 under 35 U.S.C. 112, second paragraph, as set forth at pages 3-4 of the previous Office Action (16 March 2006), is *withdrawn* in view of the amendment (21 September 2006).

The rejection to claims 57-66 under 35 U.S.C. 112, first paragraph, scope of enablement, as set forth at pages 4-6 of the previous Office Action (16 March 2006), is *withdrawn* in view of the new rejection below.

The rejection to claims 57-66 under 35 U.S.C. 102(e) as being anticipated by Boyle, US Patent No. 5,843,678, as set forth at page 7 of the previous Office Action (16 March 2006), is *withdrawn* in view of Applicant's arguments (21 September 2006).

Claim Rejections - 35 USC § 102(e)

Claims 58, 59, 61, 62, 65, 66 (and new claims 67-70) remain rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson, US Patent No. 6,740,522 B2 in view of Tsukii *et al.,* Biochemical and Biophysical Research Communications 246:337-341 (1998). The basis for this rejection is set forth at pages 8-9 of the previous Office Action (16 March 2006).

Applicant argues that Anderson teaches immunization against RANKL (aka OPGL), but not immunization of an autologous host with OPGL, as claimed in the present invention. Applicant discusses Anderson *et al.* Applicant concludes that a POSITA would believe that immunizing with RANKL/OPGL would inhibit RANKL (OPGL) and thereby inhibit the immune response because T cells are the key cells in the control of antibody producing B cells. Applicant argues that a POSITA would believe that vaccination against RANKL/OPGL, a stimulator of the immune system, would lessen the strength of any immune response via the inactivation of RANKL/OPGL and would have no expectation of success. Applicant maintains that the present inventors were the first to realize and demonstrate that it is possible to obtain a relevant effect by actively immunizing against RANKL (OPGL). Applicant argues that the Tsukii *et al.* reference discloses studying the effect of rabbit alpha-OPGL antibody (raised with a fragment of the mouse OPGL protein) on bone resorption in a mouse long bone culture system, a non autologous system.

Applicant's arguments have been fully considered but are not deemed persuasive. The specification defines "autologous" to mean self. Anderson *et al.* teach that RANKL proteins are useful in augmenting an immune response such as a vaccine

adjuvant (column 10, lines 51-62). Anderson *et al.* teach that RANKL may be administered to an individual as a vaccine adjuvant (column 15, lines 64-66). A RANKL vaccine would interfere with the action of RANKL/OPGL via antibodies made against the protein in a subject (i.e. down-regulate autologous OPGL). Anderson *et al.* teach that RANKL can be used as an immunogen to generate antibodies, which are useful in interfering with RANKL signaling; antagonistic or blocking antibodies (column 22, lines 44-50). Applicant does not provide any scientific evidence to support the assertion that vaccination against RANKL/OPGL, would *lessen* the strength of any immune response via the inactivation of OPGL or that there is no expectation of success. Claims 58 and 59 are drawn to down-regulation of autologous OPGL in an individual comprising administering an immunogenic agent capable of inducing an immune response, which Anderson *et al.* teach. The Tsukii *et al.* reference was used to teach the correlation between RANKL/OPGL and bone resorption. Tsukii *et al.* teach osteoclast differentiation factor (ODF) as a ligand for osteoprotegerin (OPG) and that ODF is identical to RANKL (page 337, 2nd paragraph). Thus, RANKL/OPGL and ODF are the same protein. Tsukii *et al.* teach that ODF induced bone resorption in fetal mouse long bone and antibodies against ODF suppressed bone resorption. The motivation and expected success is provided Anderson and Tsukii *et al.* Anderson *et al.* teach that RANKL may be administered to an individual as a vaccine adjuvant and that RANKL can be used as an immunogen to generate antibodies, which are useful in interfering with RANKL signaling; antagonistic or blocking antibodies. Tsukii *et al.,* teach that

antibodies against ODF (i.e. RANKL/OPGL) inhibit bone resorption. The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

NEW CLAIM OBJECTIONS/REJECTIONS

Claim Rejections-35 USC § 112, First Paragraph, Written Description (New Matter)

Claims 67-70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The specification as originally filed does not provide support for the invention as now claimed: "to a subject at risk" (claims 67 and 68).

Applicant's amendment, filed 21 September 2006, asserts that no new matter has been added and directs support to page 1, line 11-page 2, line 18, for the written description for the above-mentioned "limitations". The wording or connotation of the instant claim(s) is not readily apparent from said sections.

The specification as filed does not provide a written description or set forth the metes and bounds of this "limitations". The instant claims now recite limitations which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as-filed.

Applicant is required to cancel the new matter in the response to this Office action. Alternatively, Applicant is invited to provide specific written support for the

"limitations" indicated above or rely upon the limitations set forth in the specification as filed.

Claim Rejections-35 USC § 112, First Paragraph, Scope of Enablement

Claims 58, 59, 61, 62, 65-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method for down-regulation of autologous OPGL or treating, ameliorating a disease in an individual in need thereof comprising administering **a OPGL polypeptide vaccine or a OPGL nucleic acid vaccine,**

does not reasonably provide enablement for:

a method for **preventing a disease** in an individual **OR** comprising administering **an immunogenic agent, live vaccine or a viral vaccine..**

The subject matter sought to be patented as defined by the claims is not supported by an enabling disclosure because the specification fails to teach how to make and use "any immunogenic agent" to induce an immune response and down-regulate autologous OPGL in an individual. The term "an immunogenic agent" encompasses a large genus. The instant specification fails to indicate that a representative number of structurally related compounds are disclosed and therefore, the artisan would not know the identity of a reasonable number of representative compounds falling within the scope of the instant claim and would not know how to make them. The specification does not address how to make and use any immunogenic agent (e.g. chemicals, compounds, nucleic acid, lipids, macromolecules, etc) that is

capable of inducing an immune response against the subject's autologous OPGL. Furthermore, the examples from the specification teach the construction of OPGL protein vaccines. However, it could not be predicted that the instant data presented in the specification would be in any way correlative with administration of any immunogenic agent. The immunogenic agent should ONLY recognize endogenous OPGL to induce an immune response. Any immunogenic agent, capable of inducing an immune response against the subject's autologous OPGL, could also down-regulate other autologous proteins in an individual. The specification fails to disclose examples demonstrating that upon administering any immunogenic agent, antibodies against the immunogenic agent will result in *in vivo* down-regulation of **solely** endogenous OPGL activity .

As was stated in the previous Office Action (16 March 2006), the specification fails to teach how to *prevent* a disease characterized by excessive bone resorption and fails to teach how to administer a live vaccine and/or viral vaccine encoding OPGL. The Examiner submitted reference which teach the problems associated with the use of live bacterial carriers such as reversion to virulence, horizontal gene transfer, host genetic factor, immune responses, accommodation of heterologous DNA, safety concerns, lyophilization and/or host cell range of vaccine vectors.

Due to the large quantity of experimentation necessary to prevent a disease characterized by excessive bone resorption from occurring in a subject, the large quantity of experimentation necessary to generate live and/or viral vaccines encoding OPGL and screen same for activity, the large quantity of experimentation necessary to

demonstrate that any immunogenic agent will produce antibodies that recognize and down-regulate only endogenous OPGL, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of live bacterial and viral vectors, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Applicant argues that the USPTO issues patents having wordings similar to the wording of the present pending claims [method of preventing]. Applicant cites patents. Applicant argues that the level of skill of a person of ordinary skill in the art (POSITA) is high in the biotech/medical field and that a skilled clinician would never utilize a pathogenic virus or bacterium not only because of their knowledge as a POSITA, but also because regulatory approval would never be obtainable for such a vaccine vector. Applicant maintains that the present specification provides appropriate guidance by reciting that non-pathogenic vectors should be used. Applicant argues that the specification refers directly to standard textbooks dealing with the subject of preparing live vaccines. Applicant cites references in the specification. Applicant contends that based on the disclosure of the present application, a POSITA, is able to practice the present invention, without undue experimentation.

Applicant's arguments have been fully considered but are not deemed persuasive. In response to Applicant's arguments regarding methods of preventing, each patent application is examined on its own merits. What was allowable in one

Patent has no bearing on this Application. In response to Applicant's arguments regarding live and viral vaccines, the scope enablement issue is judged against the well-established Wands factors. The key issues in the instant case are the nature of the invention, the state of the prior art, the amount of direction provide by the inventor and the existence of working examples. The state of the prior art provides evidence for the degree of predictability in the art and is related to the amount of direction needed in the specification. The more that is known in the prior art about the nature of the invention, the more predictable it is and the less information is needed. If one skilled in the art can readily anticipate the effect, than there is predictability in the art. As was shown in the references submitted in the previous Office Action, there is high degree of unpredictability in the art of administered live and viral vaccines. A considerable amount of time is permissible for the quantity of experimentation needed to make or use the instant invention based on the disclosure. However this depends on if the invention is routine or if the skilled artisan is given sufficient direction or guidance. In the instant case, the experimentation is not routine and Application has provided no guidance beyond the mere presentation of cited references. Lastly, the instant specification fails to disclose working examples of administered live or viral vaccines encoding OPGL. The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. Lack of working examples, however is a factor to be considered, especially in a case involving an unpredictable and undeveloped art. The evidence as a whole leads the Examiner to conclude that undue experimentation would

be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections-35 USC § 112, First Paragraph, Written Description

Claims 58, 59, 61, 62, 65-70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

There is insufficient descriptive support for the genus "an immunogenic agent". An immunogenic agent can encompass, lipids, antibodies, nucleic acids, chemical analogs, biomolecules, macromolecules, etc. The instant method requires the use of undisclosed agents. The specification does not demonstrate possession of the instant process steps, which require the use of undisclosed immunogenic agents. No structural characteristics of such immunogenic agent are provided, nor is there any indication that applicant had possession of any immunogenic agent. The instant claims are drawn to a genus of immunogenic agents based entirely on function.

> Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

The skilled artisan cannot envision the detailed chemical structure of the encompassed immunogenic agent, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

There is insufficient descriptive support for the genus "immunogenic agent". Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 58, 59, 61, 62, 65-70 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2 and 15 of U.S. Patent No. 6,645,500 B1 in view of Tsukii *et al.,* Biochemical and Biophysical Research Communications 246:337-341 (1998) (reference of record).

The instant claims are drawn to a method for down-regulation of autologous OPGL or treating, ameliorating or preventing disease in an individual characterized by excessive bone resorption comprising administering an immunogenic agent capable of inducing an immune response (or antibody response) against the subjects' autologous OPGL. The instant claims are also drawn to adjuvants.

The claims of U.S. Patent No. 6,645,500 B1 are drawn to a method for *in vivo* down-regulation of osteoprotegerin ligand (OPGL) activity in an animal comprising effecting presentation to the animal's immune system of an immunogenically effective amount of at least one OPGL polypeptide or analogue thereof which has a result that immunization of the animal with the OPGL polypeptide or analogue thereof, induces production of antibodies against the animal's own OPGL polypeptide which down-regulates the animal's own OPGL activity, wherein said OPGL polypeptide or analogue

thereof comprises the sequence of residues 159-317 of SEQ ID NO:2 or the sequence of residues 159-317 of SEQ ID NO:2 wherein at least one foreign promiscuous, immunodominant T helper lymphocyte epitope (Th), is introduced in said residues 159-317. The claims of U.S. Patent No. 6,645,500 B1 also teach adjuvants.

Although the conflicting claims are not identical, they are not patentably distinct from each other. The OPGL polypeptide or analogue thereof (species claim) administered to down-regulate an animal's own OPGL activity in US Patent 6,645,500 B1 is encompassed by the immunogenic agent administered to down-regulate autologous OPGL (genus claim) of the instant application. The species renders the genus obvious. Tsukii *et al.* teach osteoclast differentiation factor (ODF) as being identical to RANKL/OPGL (page 337, 2nd paragraph). Thus, RANKL/OPGL is ODF. Tsukii *et al.* teach that OPG inhibits osteoclast development (inhibits resorption) *in vivo* (page 337, 1st-2nd paragraph). Tsukii *et al.* teach that *in vitro* bone resorption assays based on a bone tissue culture provides a system similar to the *in vivo* tissue microenvironment (page 338, 1st paragraph). Tsukii *et al.* teach that ODF induced bone resorption in fetal mouse long bone and antibodies against ODF suppressed bone resorption induced by various factors (page 339, Discussion).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of U.S. Patent 6,645,500 B1 by formulating it for down-regulation of autologous OPGL or treating, ameliorating or preventing disease in an individual characterized by excessive bone resorption comprising administering an immunogenic agent capable of inducing an immune response (or an antibody response)

against the subject's autologous OPGL. One having ordinary skill in the art would have been motivated to make such modifications because U.S. Patent 6,645,500 B1 teach the down-regulation of OPGL activity comprising administering an OPGL polypeptide or analogue thereof to induce production of antibodies against the subjects own OPGL. Tsukii *et al.* teach that ODF (aka RANKL/OPGL) induced bone resorption in fetal mouse long bone and antibodies against ODF suppressed bone resorption.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

RMD
12/7/06

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